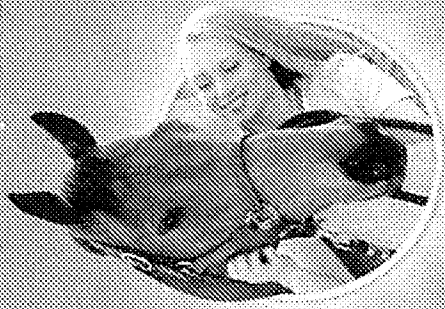


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West Nile Virus: Threat and Response

BY KAREN BRIGGS

For a demonstration of the value of vaccination, look no further than West Nile virus (WNV). When it roared onto the Eastern shore of the United States in 1999 (most likely thanks to a European or African bird), WNV struck fear into the hearts of horse owners when it quickly became clear that equines were more vulnerable to the virus than humans. Appearing more virulent than it had ever been on the other side of the Atlantic (where it had been recognized since the 1930s), WNV took full advantage of the naive immune systems of North American horses. One in three equines that contracted the disease died, and many survivors were left with lasting neurological problems.

Management beyond vaccination is important.

Editor's Note
This is the third in a 12-part series of articles on vaccinations for horses.

VACCINATION

PART 3

The virus also showed an alarming ability to spread with its avian carriers—a wide variety of birds from blue jays to crows. Mosquitoes that feasted on infected avian blood, then punctured horses with their next bite, spread WNV from species to species. From 25 equine cases documented by APHIS (Animal and Plant Health Inspection Service) of the United States Department of Agriculture in 1999, all on the Eastern seaboard, the incidence of WNV in horses more than doubled to 69 (in New England, New York, and Pennsylvania) in 2003, then skyrocketed to 733 in 2004 as West Nile virus infiltrated the warm, humid, mosquito-friendly southern states of South Carolina, Georgia, and Florida.

From there it continued its rapid spread westward, reaching Montana and New Mexico in 2002 and devastating horse populations in the central states of Texas, Oklahoma, Nebraska, Iowa, Missouri, Illinois, and Minnesota, each of which reported in excess of 800 equine cases that year.

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(see maps on page 102). All told, there were more than 15,000 cases of WNV in horses in the United States in 2002, and the westward spread was mirrored in Canada as the virus hit Manitoba, a province that suddenly saw great irony in its claim that the mosquito is the "principal bird." Of the 336 reported cases of equine WNV in Canada in 2002, 236 came from Manitoba, with the remainder in Ontario, Quebec, and Saskatchewan.

By 2004, WNV had been reported in every American state except Alaska, Hawaii, and Washington state, and it had progressed as far west as Alberta in Canada. But the overall number of cases had dropped significantly, especially in the east. In the continental United States, there were 3,181 reported cases of equine WNV in 2003, and the 2004 tally was just 1,341. Canada's numbers showed a similar trend—445 horses in 2003 and only 13 in 2004.

What caused the turnaround? Researchers speculate that climate conditions had a major impact; cooler, drier conditions in many parts of North America in the past two years just didn't favor a burgeoning mosquito population and could have affected bird migration patterns. Control measures—such as spraying and increased vigilance about cleaning up standing water where mosquitoes breed—helped too. But perhaps the most pivotal factor was the introduction of a vaccine protecting horses against WNV in August of 2001. First tracked to the market on a conditional license, Fort Dodge Animal Health's West Nile Inavivator, a killed virus vaccine, was

instantly embraced by veterinarians and owners alike.

Protection from WNV

Fort Dodge's vaccine is, in fact, the first of its kind—a vaccine for horses that hit the commercial market before a comparable vaccine was available for humans. Ordinarily, it's the other way around, with developments in the veterinary pharmaceutical market lagging months or years behind treatments and preventions for people. Fort Dodge was able to launch its recombinant response to the crisis through the use of a conditional license based on early challenge studies. By 2003, with millions of horses having received the vaccine and a strong record of safety and efficacy, it was granted full approval by the USDA.

W. David Wilson, BVMS, MS, professor of equine internal medicine and associate director of the large animal clinic in the Veterinary Medical Teaching Hospital at the University of California, Davis, explains, "In order to get a conditional license for a vaccine, you have to demonstrate (that the disease is) an imminent threat, and you have to demonstrate a reasonable expectation of efficacy and safety. Because West Nile virus is similar in many ways to the viruses for Eastern and Western equine encephalitis (EEE and WEE), formulating a vaccine for WNV wasn't much different than formulating those vaccines. Basically they killed the (inactive) bug, added the adjuvant, and the vaccine was ready for testing, with expectations that it would perform similarly to those EEE and WEE

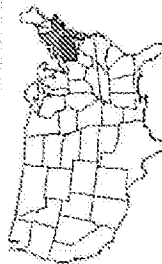


Even if vaccination has vastly reduced the incidence of WNV in horses, remember that the infection rate in mosquitoes is still high.

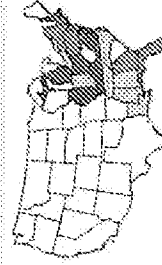
WEST NILE VIRUS: MARCH ACROSS THE UNITED STATES



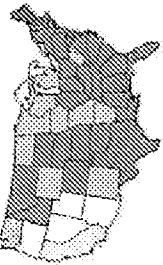
1999
Twenty-five equine cases of West Nile virus (WNV) were documented in 1999, all on the Eastern seaboard.



2003
The incidence of WNV more than doubled to 69 equine cases in 2003 in New England, New York, and Pennsylvania.



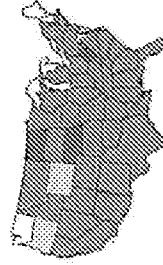
2004
As WNV infiltrated the warm, humid, mosquito-friendly southern states of South Carolina, Georgia, and Florida, the number of equine cases skyrocketed to 733.



2002
As WNV continued its rapid spread westward, Montana, Washington state, Idaho, and New Mexico reported equine cases, and horse populations in the central states of Texas, Oklahoma, Nebraska, Iowa, Missouri, Illinois, and Minnesota each reported in excess of 800 cases. In total, there were more than 15,000 equine WNV cases in 2002.



2001
In the continental United States in 2001, there were 5,181 WNV equine cases reported.



2004
By 2004, WNV had been reported in every continental American state.

- Shaded areas indicate:
 - Birds, mosquitoes, horses
 - Birds, horses
 - Horses, mosquitoes, humans
 - Horses, mosquitoes
 - Humans, horses
 - Humans, mosquitoes

vaccines, which had already been proven very successful."

At the time researchers at Fort Dodge began their investigation into creating an equine West Nile vaccine, the disease had affected fewer than 100 horses in the United States. "You have to applaud them for taking the gamble," says Wilson. "When West Nile first showed up here, many predicted it was going to be no big deal as it generally is on the other side of the Atlantic. Few expected it would sweep across the continent the way it did or be so virulent. Fort Dodge thought otherwise, and their fast action certainly has paid off. I don't think there's anyone who's not grateful for the availability of that vaccine."

Kevin Hardins, DVM, MDA, assistant professor at Kansas State University and field veterinary consultant for Fort Dodge Animal Health, notes, "The demand (for West Nile Inavivator) was greater than we anticipated in 2001, but fortunately we were able to keep up. By 2002, it was in widespread use in the United States and had also been approved in Canada. By 2003, we saw cases of West Nile in horses drop dramati-

cally. That's pretty good evidence of efficacy, along with our challenge studies that demonstrated a 96% protection rate (against viremia), so it was relatively easy to get full approval for the vaccine in 2003."

There was, however, a blip on the radar that never had an impact on the USDA, but did temporarily make some horse owners hesitant to use the Fort Dodge vaccine. In 2003, a few individuals calling themselves the "Lost Foals Group" alleged that administering the West Nile virus vaccine to their broodmares had caused them to abort or have deformed foals. The accusation got some mainstream media attention in the *Denver Post*, and nervous horse owners started to question their veterinarians about the safety of the vaccine. Many reputable veterinarians spoke up in support of the safety and efficacy of Inavivator, while closer examination of the circumstances of the admittedly unlucky breeders of the Lost Foals Group revealed no substantiation for their claims.

"It was a lot of noise for a while there," says Hardins, "and it didn't really have an effect on sales because vets didn't buy into suggesting that there's no known risk in

it. But it did make the USDA and APHIS do something they normally don't do: They posted messages on their web sites supporting the use of Inavivator in horses and emphasizing the importance of vaccination against West Nile."

A recently completed retrospective study from Texas A&M University examining the vaccination history of 595 broodmares now confirms that there is no link between the Inavivator WNV vaccine and reproductive problems, although like many vaccines, West Nile Inavivator is not specifically labeled for use in pregnant mares.

"Use it at your veterinarian's discretion," says Hardins.

More discretion is needed regarding vaccination frequency. West Nile Inavivator is labeled for one-year duration of immunity to help prevent viremia, but many veterinarians recommend giving it more often where mosquitoes are active year-round. "It's very important to communicate with your veterinarian to develop a protocol for your individual horses and your individual circumstances," Hardins emphasizes, while suggesting that there's no known risk in

First West Nile Virus DNA Vaccine for Mammals on the Way

A new vaccine to protect horses against West Nile virus (WNV) has been developed and submitted for USDA review. If approved, it would be the first commercially available DNA vaccine for any mammalian or animal species.

Steve Chu, DVM, PhD, senior vice president of Global Research and Development at Fort Dodge Animal Health, explained the concept of a DNA vaccine. The vaccine has two major components—one is a piece of DNA that codes for two West Nile viral proteins (the membrane protein and the envelope protein), and an adjuvant, which helps stimulate immune response.

In a conventional killed-virus vaccine, "We prepare the viral proteins in the manufacturing plants and put them in the final product as the antigen," said Chu. "Most animals that have received conventional WNV vaccines will create an immune response to the protein antigens and become protected."

Chu explained the novel DNA vaccine. "DNA is the genetic code of life. Once it's given to a host animal in a vaccine, it will be taken up by the host's cells. The DNA (of the diseases you want to protect against) molecules need to get inside an animal's cells—in this case, they could be picked up by the muscle cells, and they can then make the muscle cells go through further life cycle changes and be processed, or transcribed, into RNA. That RNA then can be translated into proteins. The proteins can be used to stimulate antibodies and a lymphocyte (white blood cell) immune response," Chu protecting the horses from disease.

This WNV DNA vaccine technology also differs from another vaccine that has been on the market about a year. That canarypox

ACQUAINTANCE

PART 3

vaccinating more often. "It's an extremely smooth vaccine with less than a 0.01% incidence of reactions reported in our challenge trials," he adds.

With WNV the new disease focus for many horse owners, veterinarians noticed an unsettling phenomenon in 2004. A spike in the incidence of EEE in unvaccinated horses in the eastern United States. Researchers speculate that many owners might have forgotten to vaccinate for this long-standing, very dangerous disease, which has double the mortality rate of WNV. So, it's timely that Fort Dodge now formulates the West Nile-fortior vaccine in various combinations. Depending on your location and the recommendations of your veterinarian, you can now give a single injection to protect against other encephalitis such as WEE, VEE, and/or EEE. In addition to West Nile virus, "We call it the mosquito shot," says Hankins. There's also a combination vaccine that includes tetanus.

March 2005

vaccinated vaccine (by Merial) is a recombinant viral vaccine, not a DNA vaccine. Canarypox is used to carry West Nile virus genes into the horse's cells to stimulate immunity.

DNA vaccines are relatively new to science—the very first DNA vaccine concept was presented in 1992, while conventional vaccine concepts were presented over 100 years ago. The Food and Drug Administration approved the first DNA vaccine protocol for use in human trials in 1995. While thousands of DNA vaccine research papers have been published, no vaccine has been approved for commercial use in humans or any other animal species, so Chu's knowledge.

All commercial animal vaccines must be independently approved by the USDA for purity, potency, efficacy, and safety. "Certainty, significant protection and safety would need to be demonstrated to make an acceptable to the USDA—solely to the horses, handlers, and the environment," he said.

The WNV DNA vaccine will be administered much like the other WNV vaccines available—two initial doses given approximately three to four weeks apart.

"We don't expect the use of this product will be fundamentally different than how people are used to protecting their horses," said Chu. According to Chu, Fort Dodge's DNA vaccine is in the late stages of the USDA approval process, and he hopes it will become available during 2005. Detailed efficacy and safety information will be available for the public until that time.

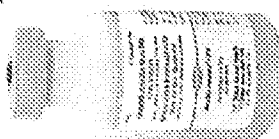
"This certainly represents an additional new technology that could be made available for disease protection," Chu concluded.

—Stephanie L. Christ

any horse receiving a West Nile fortior vaccine for the first time should get two injections three to six weeks apart. Thereafter, a single booster yearly (ideally administered a couple of weeks before mosquito activity begins) should provide good protection. Naïve horses that receive only one West Nile fortior shot can launch a rough of an immune response to protect them to some degree—in studies, such horses sometimes contracted the disease on exposure, but experienced milder symptoms. But if you administer the first shot and miss that three- to six-week window, Hankins recommends you "start over" with a course of two shots in order to ensure the best protection for your horse.

RECOMBITEK, it's now available in the United States and Canada.

The difference between the Fort Dodge and Merial vaccines is that RECOMBITEK is a recombinant vaccine that piggybacks a couple of antigenic proteins from WNV on a canarypox vector. The WNV proteins are just enough to stimulate immunity with no danger of provoking disease symptoms in the horse. As for the canarypox, Stephanie Thompson, DVM, manager of technical services for Merial, explains, "Canarypox is like a shuttle bus, carrying the information the horse needs to stimulate his immune response. The canarypox is alive, but it's completely benign to horses. It attempts to replicate in the horse's cells, but it can't complete the process and it dies. So, the horse will not develop a neutralizing immune response against the canarypox, meaning there'll be no problem using the vaccine over and over in the same animal."

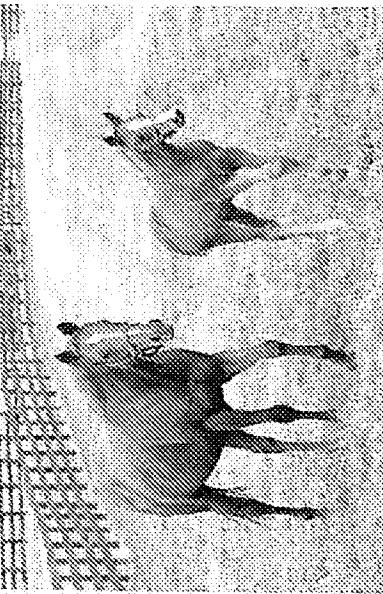


Fort Dodge's vaccine is the rarest of creatures—a vaccine for horses that hit the commercial market before a comparable vaccine was available for humans.

Something Old, Something New

Fort Dodge had no competitor in the marketplace with regard to WNV vaccines until January of 2004. That's when Merial Ltd. launched, with full

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A study from Texas A&M University examining the vaccine history of 595 broodmares now confirms that there is no link between the West Nile fortior vaccine and reproductive problems, although like many vaccines, it is not specifically labeled for use in pregnant mares.

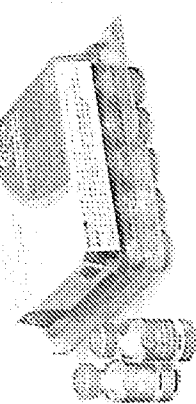
Although RECOMBITEK represents the first use in North America of a recombinant canarypox vaccine for horses, it's not the first one based on canarypox in Merial's arsenal. Merial markets an equine influenza vaccine based on the same technology in Europe, and it has several canarypox vaccines available for small animals on this continent. There's even a canarypox vector distemper vaccine for ferrets, and a very well-received one used in zoos for giant pandas, which are vulnerable to distemper.

"Canarypox is an extremely safe and effective vector," Thompson says. "It's very specific to canaries and their close relatives. One of the most unique things about recombinant technology is that you stimulate both the humoral immunity (when B lymphocytes are activated by the presence of an antigen, they transform into plasma cells that produce antibodies against the antigen) that a killed vaccine would stimulate, and cell-mediated immunity (the part of the immune system that produces 'killer' cells that directly attack foreign invaders), so you get a more complete immune response. And they also seem to give a more rapid onset of immunity than you'd see with a killed vaccine."

"According to our trials," she continues, "Merial's vaccine against West Nile virus piggybacks a couple of antigenic proteins from the WNV on a canarypox vector; the proteins are just enough to stimulate immunity with no danger of provoking disease symptoms in the horse."

Thompson says that the vaccine is safe and effective, and it's not specifically labeled for use in pregnant mares.

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Fort Dodge's vaccine is the rarest of creatures—a vaccine for horses that hit the commercial market before a comparable vaccine was available for humans.

that in mosquito-endemic areas, veterinarians might recommend using it more frequently. There have been no reported safety concerns with frequent use. RECOMBITEK will likely be available in combination vaccines sometime in 2005.

What's Next for WNV?

Those watching WNV's progress across the North American continent could be excused for hoping its westward march might just take it straight out to sea in 2005, never to be heard from again. Unfortunately, say experts, that's not likely. WNV has been considered an endemic disease in the United States since late 2002, lurking in bird and mosquito populations and causing occasional outbreaks in unvaccinated horses, as does EEE.

"[I]f take us another few years to really be able to predict what it's going to do, though," says Thompson. "We're still trying to put together models that work."

Anyone who makes predictions about (the behavior of) West Nile virus is foolishly, says Wilson. "The only thing I can say for sure is that I believe it's here to stay."

"It depends so much on the climate, which affects bird migratory pathways, populations of mosquitoes, and the amount of contact between birds and mosquitoes," Wilson continues. "Even if vaccination has vastly reduced the incidence of West Nile in horses, we have to remember that the infection rate in mosquitoes is still high, so the virus remains active in the reservoir population. It's just not spilling over into horses as much now."

So much about the behavior of WNV remains unexplained—including how it got to North America in the first place, why it spread so quickly, and why it's so much more virulent here than in its place of origin. Handling specialists, "I might have a lot to do with the species of mosquitoes that carry it here, and with the migration patterns of the birds that spread it."

"What I'd hate to see happen is people deciding West Nile is no longer a problem, so they stop vaccinating for it," says Thompson. "All in all, vaccines are pretty cheap insurance." ■

Kevin Hedges was for more than 20 years a veterinarian in Canada, the United States, and Great Britain. Hedges is now a freelance writer and editor. He has written for many national and international publications, including The Horse, published by Equi Media and distributed by Newsweek and Time Inc. He can be reached at k.hedges@equi.com or 508.885.5545.